REMARKS

Applicants wish to thank Examiner Lin for the helpful interview with Dr. Neal Gordon, President of the assignee of this application, and Applicants' representative, Edmund Pitcher, on Thursday, April 26, 2007. During the interview, various issues and options were discussed. Attorney Pitcher discussed at length his view that the outstanding obviousness rejections were improper under prevailing interpretations of 35 U.S.C. §103. Specifically, Attorney Pitcher indicated that the references identified by the Office did not disclose or suggest the subject matter claimed by Applicants, *taken as a whole,* but rather simply amounted to art teachings of some, but not all, of the claimed elements of Applicants' invention, and that none of the references seek to address the problem that Applicants have solved.

As discussed in the interview, Applicants have amended the independent claims in this application to put the application in condition for allowance. Attorney Pitcher respectfully requests that Examiner Lin call him (office 617-570-1780, cell 617-840-7767) if there are any unresolved issues which need to be addressed before mailing a Notice of Allowability or Notice of Allowance. Claim 9 has been canceled and its respective element added to independent claim 1. Each of independent claims 30 and 42 have been amended to incorporate a similar element. Basis for these amendments appears, for example, at page 35, line 6. Additionally, Applicants have amended claims 1 and 42 for clarity.

35 U.S.C. § 112, Second Paragraph Rejections

Claims 1-9, 13, 19-21, 23, 24, 26-28, and 47 were rejected under 35 U.S.C. § 112, Second Paragraph, based on alleged indefiniteness of the phrase "at least one of which... " in claim 1, step (1). Applicants respectfully submit that this phrase is intended to have its ordinary meaning, consonant with traditional English grammar, and is intended to refer to proteins under analysis: ". . . a plurality of target proteins in a biological sample, at least one of which comprises . . ."

Claim 9 was rejected based on alleged indefiniteness of the phrase "amino acid

sequence" as comprising a splice junction. Applicants have herein cancelled claim 9. To the extent that similar language has been incorporated into independent claims 1, 30, and 42, Applicants have used the phrase "amino acid sequence encoded by an RNA comprising a splice junction" to address the concern in the Office Action.

Accordingly, Applicants respectfully request reconsideration and withdrawal of these rejections.

Rejections Under 35 U.S.C. § 103(a)

Claims 30-34 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over United States Patent Application Publication No. US 2002/0137119 by Katz ("Katz") in view of Kohlberger *et al.* (1997) Gynecologic Oncology 66: 227-232 ("Kohlberger"). Claims 1, 3-5, 7-9, 19, 21, 24, 28, 42, 44, and 46 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over Katz in view of Kohlberger, further in view of United States Patent No. 5,955,317 by Suzuki ("Suzuki"). Claims 1-9, 13, 19-21, 23, 24, 26-28, and 44-47 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over Katz in view of Kohlberger in view of Suzuki, further in view of United States Patent No. 6,897,073 by Wagner *et al.* ("Wagner"). Applicants respectfully request reconsideration and withdrawal of these rejections in view of the present amendments and following remarks.

The claimed subject matter of the present invention enables the measurement of proteins in a sample that includes one or more proteins that are expression products of an alternative splicing form of DNA. Sample proteins are fragmented using a predetermined protocol to generate peptide epitope tags (PETs) that are unambiguously indicative of the target proteins in the sample. As amended, the independent claims of the present invention require that a PET from a protein expressed from a splice variant comprises an amino acid sequence encoded by RNA comprising a splice junction. Capture agents on an addressable array selectively interact with the PETs to allow for detection of the target proteins in the sample, including expression products of splice variants. Accordingly, for the target proteins with PETs comprising an amino acid sequence encoded by an RNA comprising a splice junction, detection is facilitated by identification of the amino acid sequence corresponding to the splice junction. Indeed, by using

a combination of such capture agents, each directed to an amino acid sequence encoded by RNA from two adjacent exons, all splice variants can be detected and distinguished from one another.

For example, consider a sample wherein protein A_1 comprises the product of the DNA sequence exon A - intron - exon B; protein A_2 comprises the product of the DNA sequence exon A - intron - exon C; and protein A_3 comprises the product of the DNA sequence exon B - intron - exon C. The method of the present invention allows for the unambiguous identification of each protein product by detecting, for example, the splice junction between the exons. By comparison, detection of exon A, or exon B, or exon C alone would not allow for the unambiguous identification of any of proteins A_1, A_2, or A_3. Applicants respectfully submit that none of the cited references, alone or in combination, describe at least this feature of the present invention.

Rather, Katz provides a method for generating novel peptide antigens which are capable of inducing the production of protein-specific antibodies which can be used to detect the protein in samples, which contain low protein concentrations and/or low exposure of protein-specific antigenic regions. Paragraph 59. With respect to detecting protein products of splice variants as required by the claims of the present invention, Katz is silent.

Kohlberger discloses the histoanalysis of proteins in fixed tissue using antibodies "specific for CD44 splice variants." Paragraph bridging pages 229-230. Kohlberger fails to teach or suggest the step of generating from a protein expressed from a splice variant a PET that comprises an amino acid sequence encoded by RNA comprising a splice junction, as required by the claims of the present invention, as amended.

Suzuki discloses a panel of antibodies for determining the presence of 40 amino acid and 42 amino acid beta amyloid protein isoforms. These isoforms do not correspond to splice variants (see, e.g., http://www.upstate.com/features/app_lp.asp -- Amyloid Precursor Protein (APP) and Amyloid β (Aβ)). Rather, the multiple APP isoforms, generated by alternative splicing, have been described with a 770 amino acid isoform being the largest and a 695 amino acid isoform being most prevalent in neuronal cells. Sequential proteolytic processing of the 695 amino acid isoform of APP give rise to the Aβ peptides, known as Aβ x-40, x-42 and x-43 for the number of amino acids they contain. While they are produced by the cleavage of one of the

10 or so different splice variants, they are not themselves splice variants. Thus, rather than being expressed from different RNAs spliced from the same DNA, a larger protein expressed from a single RNA is differentially cleaved at its C-terminus to produce either the 40 AA or the 42 AA form. Accordingly, Suzuki fails to teach or suggest the step of generating from a protein expressed from a splice variant a PET that comprises an amino acid sequence encoded by RNA comprising a splice junction, as required by the claims of the present invention, as amended.

Wagner describes arrays of protein-capture agents and methods of using them to assay in parallel a multitude of proteins expressed by a cell or population of cells in an organism, including up to the total protein content of a cell. Column 2, lines 63-67. With respect to detecting products of splice variants, Wagner is silent.

Applicants respectfully submit that neither Katz, nor Kohlberger, nor Suzuki, nor Wagner, teach or suggest all of the elements of the present invention, as claimed. For example, none of these four references, alone or combination, teach or suggest the step of generating from a protein expressed from a splice variant a PET that comprises an amino acid sequence encoded by RNA comprising a splice junction, as required by the claims of the present invention, as amended. For at least this reason, Applicants respectfully request reconsideration and withdrawal of each of these obviousness rejections.

In addition, Applicants respectfully submit that the Office Action's suggestion to modify Katz in accordance with Kohlberger, and then in accordance with Suzuki, and then in accordance with Wagner, to find obviousness arises from impermissible, albeit unintentional, hindsight reconstruction of Applicants' claimed invention using terms selected from Applicants' claims. There is nothing in Katz to suggest use of a second capture antibody, and nothing to suggest that splice variant proteins can or should be detected. None of the secondary references in any way suggest a problem or possible modification that would lead a person of skill in the art to Katz, and vice versa. Applicants submit that modifying the primary Katz reference in accordance with Kohlberger and Suzuki and Wagner changes the essential function of the method described in Katz and renders the Katz method unsatisfactory for its intended purpose.

This hindsight reconstruction and modification that renders Katz's method unsatisfactory for its intended purpose contradicts current law and established rules. Specifically, in its recent

decision on *KSR Int'l. Co. v. Teleflex, Inc.*, the Supreme Court reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C. § 103(a) and reiterated that a "patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men." *Citing* Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp., 340 U. S. 147, 152 (1950). Moreover, it is well accepted that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Assuming, for arguments sake, that a person with ordinary skill in the art tried to modify Katz as suggested by the Office Action, he would be required to take at least the following paradigmatic leaps to change the essential function of Katz's methods. First, he would be required to modify Katz's method to identify and include in the peptide selection the expression products of splice variants. While recognizing many different protein forms, Katz's specification is silent with respect to those arising from pre-translational modifications. Accordingly, modifying the Katz method to detect pre-translational modifications to proteins runs counter to Katz's stated function.

Next, the skilled person would be required to modify Katz's method to identify and include, in its selected peptides, certain peptides comprising amino acid sequences encoded by RNA comprising splice junctions. Yet, as noted above, none of these references teach or suggest the step of generating from a protein expressed from a splice variant a PET that comprises an amino acid sequence encoded by RNA comprising a splice junction. While Katz does suggest several parameters to consider for peptide selection, including molecular weight, amino acid composition, hydrophobicity, charge, secondary structure, heterogeneity, length, post-translational modifications, polarity, solubility, amphipathic nature, sequence, and immunogenicity, (Paragraph 76), the function of Katz's method is to provide an approach for producing peptides representative of protein that, in part, are minimally cross- reactive. However, modifying Katz in accordance with, for example, Kohlberger, would direct the skilled person to identify peptides that may include the same targets and therefore be cross-reactive. For example, in a sample as described above, in which no one protein contains a unique exon, the

resulting peptides would be cross-reactive and the method would fail to discriminate between products of different splice variants.

In addition, the artisan would be required to generate more than one capture agent for each peptide. One capture agent would need to be directed against a PET, including a product of a splice junction, and the other capture agent would need to be directed against the captured polypeptide analyte comprising the PET. Katz fails to suggest this, and, applicant submits, teaches away from such modification. Specifically, to create two antibodies to Katz's peptides, the artisan would likely be required to extend the length of Katz's peptides beyond Katz's preferred length of 5-12 amino acids. Paragraph 94. This alteration to Katz's method is in direct contradiction to the teaching of Katz and, according to Katz's own specification, would undermine the function of Katz's method. Paragraph 94.

For at least these reasons, Applicants respectfully submit that modifying Katz's method in accordance with Kohlberger and/or Suzuki and/or Wagner in the fashion suggested by the Office Action requires hindsight reconstruction that essentially changes the function of Katz's method. This conflicts with the methodology reiterated in the recent Supreme Court ruling in *KSR Int'l. Co.* and in the established precedent of *In re Gordon.*

Accordingly, because neither Katz, nor Kohlberger, nor Suzuki, nor Wagner, alone or in combination, teach or suggest at least the above-identified element of the claims, as amended, of the present invention, and because modification of Katz as described in the Office Action compromises the essential function of Katz's method, and therefore contradicts established precedent, Applicants respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

In view of the above amendments and responses, Applicants respectfully request that the rejections under 35 U.S.C. § 112, Second Paragraph and under 35 U.S.C. § 103, be reconsidered and withdrawn. Applicants invite the Examiner to contact the undersigned Attorney to discuss any remaining issues with this application.

Applicants believe that the claims are in condition for allowance. Early favorable action is respectfully solicited.

Respectfully submitted,

Date: May 17, 2007
Reg. No. 58,312

Randall D. Morin
Attorney for Applicant(s)
Goodwin | Procter LLP
Exchange Place
53 State Street
Boston, Massachusetts 02109

Tel. No.: (617) 570-1657
Fax No.: (617) 523-1231